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REVERSIBLE OVULATORY FAILURE ASSOCIATED WITH THE DEVELOPMENT OF LUTEINIZED UNRUPTURED FOLLICLES IN WOMEN WITH INFLAMMATORY ARTHRITIS TAKING NON-STEROIDAL ANTI-INFLAMMATORY DRUGS

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SUMMARY

The case histories of three young women with ankylosing spondylitis, rheumatoid arthritis and a seronegative inflammatory polyarthritis undergoing investigations for infertility are presented. In each, non-steroidal anti-inflammatory drug (NSAID) therapy was associated with the recurrent development of luteinized unruptured ovarian follicles and normal ovulation following drug withdrawal. It is suggested that NSAID therapy may be an important and frequently overlooked cause of anovulation and infertility.

KEY WORDS: Arthritis, Non-steroidal anti-inflammatory agents, Infertility, Ovulation, Luteal phase.

NON-STEROIDAL anti-inflammatory drugs (NSAIDs) are widely self-administered for the relief of musculoskeletal pain as well as being almost universally prescribed as first-line drugs for treating patients with inflammatory arthritis. Not infrequently, the recipients are women of child-bearing age. While the effects of NSAIDs on maternal and fetal physiology in pregnancy and their possible teratogenicity have been a matter for considerable concern and frequent review [1], their potential effects on female fertility have been largely ignored by physicians and rheumatologists. This paper presents the case histories of three young women with inflammatory arthritis, seeking advice about infertility, in whom NSAID therapy was associated with the recurrent development of luteinized unruptured follicles (LUFs). A LUF is a dominant follicle which fails to ovulate, but becomes luteinized and secretes progesterone. It may be defined by ultrasonography as a follicle which has reached a mean diameter of 30 mm and remains this size or continues to grow for a further 3 days [2]. This phenomenon may be an important and frequently overlooked cause of failure to ovulate in patients taking NSAIDs regularly.

Three patients who presented with infertility are discussed. All had patent fallopian tubes and their partners had normal semen analyses. Three ovarian cycles were monitored in each patient. In the first cycle, the patients continued NSAID therapy and in the third cycle the NSAID was discontinued in the periovulatory period. Blood was taken for baseline serum follicle-stimulating hormone (FSH), luteinizing hormone (LH) and oestradiol levels to exclude other ovulatory disorders. Urine samples were obtained regularly throughout the cycle for LH and pregnanediol; a sharp rise in LH followed 1 week later by a pregnanediol:creatinine ratio >0.5 are considered biochemical markers of ovulation. Daily transvaginal ultrasound scans were performed, and serum oestradiol and LH were measured from day 10 until ovulation had occurred or a LUF was diagnosed. Serum progesterone was measured 7 days after the LH surge for further biochemical evidence of ovulation. A level >30 nmol/l is considered indicative of ovulation, but lower levels may suggest the possibility of ovulation.

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CASE REPORTS

Case 1

A 30-yr-old woman with an 8 yr history of ankylosing spondylitis had a 1 yr history of primary infertility. She had a regular menstrual cycle, normal baseline FSH, LH, prolactin and testosterone concentrations, and both ovaries appeared normal on transvaginal ultrasonography. Medication was naproxen 500 mg bd and sulphasalazine 500 mg bd.

During the first monitored cycle in which she took her normal medication, there was an LH surge on day 13 when there was a 15×18 mm ovarian follicle (Fig. 1). This grew to a diameter of >30 mm on day 17 (Fig. 2). Serum progesterone on day 20 was 15.8 nmol/l, which is lower than expected for an ovulatory cycle. In the second cycle, during which she took naproxen continuously, the LH surge occurred on day 16 when there was a 17×16 mm dominant follicle. This increased to >30 mm in diameter on days 20–22. The serum progesterone level on day 23 was rather low at 13 nmol/l, and not indicative of ovulation. Naproxen was discontinued from day 8 in a third cycle. An LH surge occurred on day 13, when there was a 20×21 mm dominant follicle (Fig. 3). An ultrasound scan on day 14 showed that the follicle had shrunk to 12.5 mm in diameter, presumably due to ovulation.

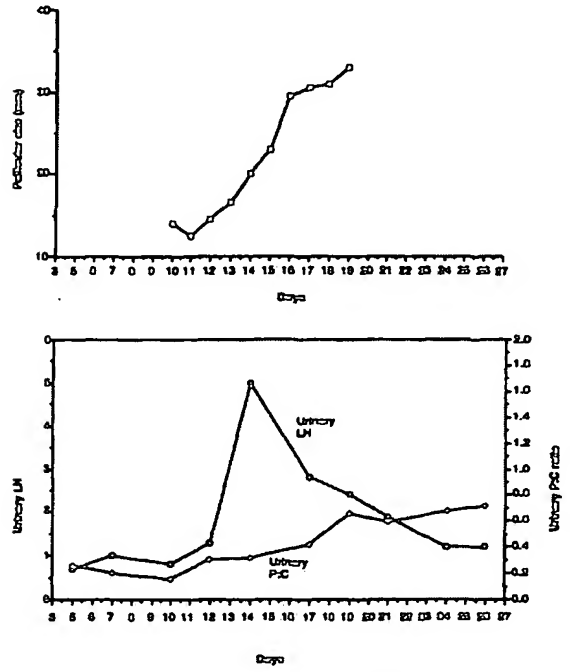

FIG. 1.—Follicular size, urinary leutinizing hormone (LH) and urinary pregnanediol:creatinine (P:C) ratio in first monitored cycle of patient 1 when naproxen was taken throughout the cycle.

Case 2

A 35-yr-old woman who had had seronegative rheumatoid arthritis for 9 yr had a 3.5 yr history of secondary infertility. Piroxicam and hydroxychloroquine were discontinued prior to her first pregnancy, and were recommenced after delivery.

Eighteen months later, she wished to have a second child. Hydroxychloroquine was stopped, but she continued to take piroxicam. A few months later she developed a myopathy secondary to hypothyroidism [thyroxine 6 pmol/l; thyroid-stimulating hormone (TSH) 73 mU/l; thyroid microsomal antibodies 1/6400] and thyroxine replacement therapy was commenced. One year later she had still not conceived. Investigations revealed that she was euthyroid, but had an elevated prolactin of 907 U/l. The hyperprolactinaemia was treated with bromocriptine and her cycles were monitored to see whether she had LUF syndrome related to piroxicam.

In the first cycle she continued to take piroxicam. An LH surge on day 24 was associated with a 22.5 mm diameter dominant follicle which remained the same size for the next 6 days. Serum progesterone on day 28 was 25.3 nmol/l, which was consistent with ovulation, but the ultrasound findings indicated that it was caused by luteinization of the unruptured follicle. A second cycle was monitored in which piroxicam was omitted from day 8. A dominant follicle at the time of the LH surge on day 13 measured 19.5 mm in diameter. Two days later, this follicle had ruptured. A third cycle was monitored in which piroxicam was again omitted from

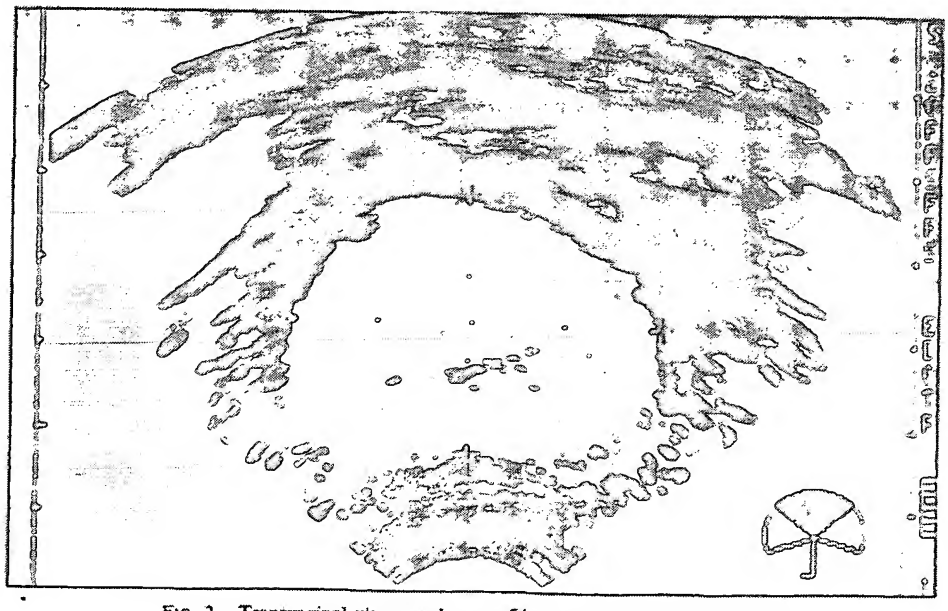

FIG. 2.—Transvaginal ultrasound scan of luteinized unruptured follicle.

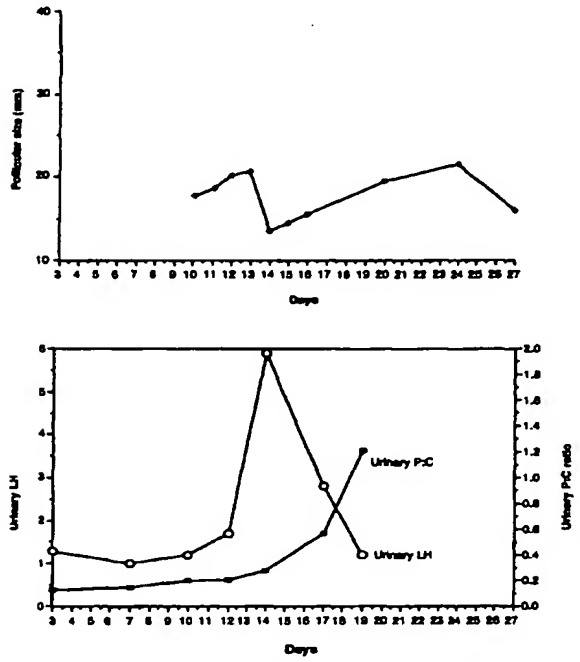

FIG. 3.—Follicular size, urinary luteinizing hormone (LH) and urinary pregnanediol:creatinine (P:C) ratio in third monitored cycle of patient 1 when naproxen was discontinued after day 8.

day 8, but during which she took sulphasalazine 500 mg four times a day throughout the cycle.

The dominant follicle measured 22.5 mm in diameter at the time of the LH surge on day 12. This follicle had shrunk considerably on a scan 2 days later. Serum progesterone on day 19 was 51.9 nmol/l which, together with the ultrasound findings, is indicative of ovulation.

Case 3

A 28-yr-old woman with a 12 yr history of seropositive rheumatoid arthritis had an 8 month history of primary infertility. Previous drug therapy had included hydroxychloroquine, sulphasalazine and penicillamine, which were discontinued either due to loss of effect or adverse reactions. She was subsequently treated with methotrexate for almost 3 yr, but this was discontinued when the couple wanted to start a family. At the time of her referral to the gynaecologists, she was taking diclofenac 200 mg daily and the possibility of LUFs was recognized.

Diclofenac was continued throughout the first two of these cycles. In the first cycle, the LH surge occurred on day 16 coincident with an 18 × 14 mm follicle. This follicle increased to 30 × 32 mm on day 20, after which it slowly reduced in size. The urinary pregnanediol:creatinine ratio, peaking at 1.18 on day 23, would normally be considered an ovulatory level, but the ultrasound findings indicate that it was due to a LUF. During the second cycle, the LH surge occurred on day 14 when there was a 17 × 16 mm dominant follicle. This grew to a mean diameter of 30 mm over the next 4 days. Both the urinary pregnanediol:creatinine ratio of 1.05 on day 20 and the serum progesterone of 33.9 nmol/l on day 21 would normally indicate ovulation, but again the rise in progesterone was due to luteinization of the unruptured follicle. In the third cycle, diclofenac was discontinued from day 10. The LH surge occurred on day 13 coincident with a 21 × 15 mm dominant follicle, but this had ruptured and virtually disappeared on scan the following day. The urinary pregnanediol:creatinine ratio and serum progesterone on day 20 were both compatible with ovulation.

DISCUSSION

Ovulation occurs when the wall of a mature ovarian follicle ruptures to release an oocyte. The process leading to this event begins with the selection and dominance of a single follicle. This matures under the influence of FSH to produce oestrogens from the theca cells and plasminogen activator from the granulosa cells. Plasminogen activator stimulates the conversion of plasminogen to plasmin, which converts procollagenase to collagenase and degrades the basement membrane. Collagenase degradation of the wall of the follicle results in the formation of the ovulation stigma through which the oocyte is expelled. Rupture of the follicle is triggered by an oestrogen-mediated surge of LH which independently stimulates the resumption of meiosis in the oocyte, and luteinization of the granulosa cells to form the corpus luteum. The rise in LH required to stimulate follicle rupture is, however, relatively high, so meiosis and luteinization can occur without concomitant follicle rupture and ovulation. The existence of such luteinized but unruptured follicles can be confirmed at laparoscopy by showing the absence of an ovulation stigma on the corpus luteum early in the luteal phase of the cycle [3, 4], by the demonstration of low oestradiol and progesterone levels in the peritoneal fluid [5], and by following follicular growth by transvaginal ultrasound and demonstrating absence of rupture [6, 7]. The interval between scans should be no more than 24 h.

In cases 1 and 3, the patients continued NSAID therapy during the first two cycles, and in the third cycle the NSAID was discontinued in the periovulatory period. In case 2, the patient continued NSAID treatment in the first cycle, and in the second and third cycles the NSAID was omitted in the periovulatory period. In each of the cases described, a LUF was demonstrated during the cycles in which the patients were taking an NSAID throughout the cycle, and in each case ovulation occurred when the NSAID was omitted during the periovulatory phase of the cycle. In some of the LUF cycles, progesterone levels in the second half of the cycle would have been considered indicative of ovulation. This emphasizes the importance of ultrasound scanning in the diagnosis of LUFs.

The process of follicular rupture and the activation of collagenase are prostaglandin dependent [8, 9]. Experimental administration of PGE2α induces ovulation in rabbits and this can be blocked by the administration of systemic, peritoneal or intrafollicular indomethacin [10]. Indomethacin has also been shown to inhibit ovulation in rats [11], sheep [12], rhesus monkeys [13] and humans [14]. Killick and Elstein [14] undertook a double-blind, placebo-controlled, cross-over comparison of indomethacin and azapropozone in volunteers. The drug was administered in the periovulatory period and follicular development was monitored by ultrasound. The spontaneous incidence of LUFs in drug-free cycles was 10.7%. When azapropozone, a relatively weak inhibitor of prostaglandin synthesis, was taken (2.4 g on the first day and 1.8 g on the next 4 days) the incidence of LUFs rose to 50%. With the more powerful inhibitor of prostaglandin synthesis, indomethacin (200 mg daily for 5 days), the incidence of LUFs was 100%. In both cases, NSAID therapy was begun on the day the dominant follicle reached a mean diameter of 16 mm. The authors speculated on the possible use of NSAIDs as a form of non-hormonal oral contraception, but did not discuss NSAIDs as a possible cause of infertility. Earlier studies in human volunteers had shown that aspirin 1.8 g/day did not inhibit ovulation [15], but it is likely that prostaglandin synthesis was not effectively inhibited *in vivo* at this dose.

The dose of piroxicam in the first two cases in this study was in the normal therapeutic range, while the dose of diclofenac in case 3 was slightly higher than that usually recommended. In the first case described, sulphasalazine was continued throughout the cycles. The 5-aminosalicylic acid component did not appear to affect ovulation, but the dose of sulphasalazine was modest. It is possible that the more usual therapeutic doses of 2 or 3 g daily might have an effect on ovulation. Reversible female infertility and amenorrhoea have been reported in seven patients with granulomatous bowel disease receiving treatment with sulphasalazine in normal therapeutic doses [16].

LUFs may also occur without any obvious cause and their importance as an overall cause of infertility is a matter of some controversy. Laparoscopic studies in fertile women have shown an incidence of spontaneous LUFs ranging from 9.4% [17] to 46.7% [18], but the reliability of laparoscopy in identifying the ovulation stigma has been questioned [19]. Early re-epithelialization of the stigma can lead to the false diagnosis of LUF. Several studies have shown a relatively low frequency of LUFs in regularly cycling infertile women. In a prospective ultrasound study of 183 cycles in 66 infertile women, LUFs were only found in 4.9% of cycles, and Kugu *et al.* [20] found only 10 cases of LUF in 250 women with unexplained infertility. After finding only one recurrent LUF in a single cycle in an ultrasound study of 35 cycles in eight women documented to have a LUF, Kerin *et al.* [21] concluded that LUFs were an uncommon cause of infertile cycles in potentially fertile women. By contrast, in another study, LUFs occurred in 57 out of 100 cycles in women with unexplained infertility of 3–10 yr duration, and 34% had recurrent LUFs in subsequent cycles [22].

The mechanism underlying the natural occurrence of LUFs is not fully understood. Whatever the incidence of spontaneously occurring LUFs, it is clear that anything which causes regularly recurring LUFs will be associated with infertility. The appearance of LUFs in women taking NSAIDS may relate to inhibition of prostaglandin-dependent processes involved in ovulation or possibly through inhibition of follicular smooth muscle contraction, a physiological event which has been noted in the hamster follicle prior to ovulation [23]. Further work is required to determine the incidence of recurrent LUFs in women in the reproductive age group who are taking regular therapeutic doses of NSAIDs in order to better assess the role of NSAIDs as a potential cause of infertility in women.

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